

b.) Remarks

Claim 6 has been amended in order to recite the present invention with the specificity required by statute. Claims 1-5 and 8 are cancelled without prejudice or disclaimer in order to reduce the issues and expedite prosecution. The subject matter of the amendment may be found in Table 1 (see Compound 2) at specification page 12. Accordingly, no new matter has been added.

Claim 6 is rejected under 35 USC 103(a) as being obvious over Chen (*J. Neurosci.*, Vol. 21 (2001) RC143), in view of Strong (*J. Pharm. and Pharmacol.*, Vol. 49, No. 7 (1997) 1260). In support of this rejection, the Examiner notes Chen teaches Itradefylline and caffeine are both adenosine A₂ receptor antagonists. Strong is relied on as teaching that compositions containing caffeine are effective in treating migraine. Accordingly, the Examiner contends it would have been obvious one of ordinary skill in the art to use Itradefylline to treat migraine as well.

This rejection is respectfully traversed. Prior to setting forth their bases for traversal, however, Applicants would briefly like to discuss the salient features of the Examiner's basis of rejection and, *inter alia*, the patentable nature of the present invention over the prior art.

Caffeine is well-known to show a great variety of physiochemical actions. For example, as shown Fredholm et al., Actions of Caffeine in the Brain with Special Reference to Factors that Contribute to Its Widespread Use, *Pharmacological Reviews*, Vol. 51, No. 1 (1999) 83-133 (copy provided in the accompanying Information Disclosure Statement), caffeine evidences adenosine A₁, A_{2A} and A₃ receptor antagonistic activities (see Table 3 at page 89). Caffeine is also a well-known phosphodiesterase (PDE) inhibitor

(for example, see Fig. 1 at page 88). Accordingly, caffeine is understood that caffeine is additionally an efficient vasoconstrictor (see Ishiyaku Shuppan's Medical Dictionary 2nd Edition (1998) which reports in Japanese "the smooth muscle relaxation by caffeine is explained by increased cAMP level in the tissue caused by the inhibition of PDE activities" (also cited in the accompanying Information Disclosure Statement).

As to Chen, such discloses that the CNS effects of caffeine are mediated by its antagonistic activity at the A₁ and A_{2A} subtypes of adenosine receptors (see page 1, from left column, line 2 from the bottom to right column, line 1). Chen also teaches the effects of caffeine on Parkinson's Disease (hereinafter "PD") are mimicked by several A_{2A} antagonists including Istradefylline as well as by genetic inactivation of the A_{2A} receptor.

However, Chen teaches the effects of caffeine are

not [mimicked] by A₁ receptor blockade with 8-cyclopentyl-1,3-dipropylxanthine, suggesting that caffeine attenuates MPTP toxicity by A_{2A} receptor blockade (emphasis added, see Abstract).

That is to say, Chen teaches (i) that caffeine interacts with both adenosine A₁ and A_{2A} receptors and (ii) the effects of caffeine on PD relate to adenosine A_{2A} receptors. However, Chen does not teach that the effects of caffeine on migraine relate to adenosine A_{2A} receptors. Obviously, migraine differs in kind as a disease from PD¹.

Strong teaches only that caffeine is useful for treating migraine. In this regard, Fredholm clarifies that caffeine has analgesic properties on specific types of pain including headache by exerting antinociceptive effect in the brain - - which relates to

¹ For instance, see the MeSH Database of PubMed (NCBI) cited in the accompanying Information Disclosure Statement.

antagonism of a tonic inhibitory activity of adenosine A₁ receptors (see page 104, second paragraph of left column).

Therefore, even if, as the Examiner asserts, the treating effect of caffeine on migraine relates to adenosine receptors, those of ordinary skill in the art would expect such relates to A₁ receptors and not to the A_{2A} receptors.

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns are now overcome and the claims are now in allowable condition. Accordingly, reconsideration and allowance of this application is earnestly solicited.

Claim 6 remains presented for continued prosecution.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,

/Lawrence S. Perry/
Lawrence S. Perry
Attorney for Applicants
Registration No. 31,865

FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Facsimile: (212) 218-2200

LSP\ac

FCHS_WS 4447469_1.DOC